Clostridium difficile and CMV in Inflammatory Bowel Disease

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Overview

I. Background – C. difficile
II. Impact of C. difficile on IBD
III. Diagnostic considerations C. difficile
IV. Treatment considerations
V. CMV
I. Clostridium difficile

- 1930's - Bacillus difficillis first described as part of the normal flora of neonates.
- 1974 - C. difficile recognized as complication of Clindamycin use.
- 1978 - C. difficile identified as the cause of antibiotic-associated pseudomembranous colitis in humans.
- Clinical syndrome may range from watery diarrhea, abdominal pain, pseudomembranous colitis, toxic megacolon, sepsis, colonic perforation and death


C. difficile: Changing spectrum of clinical disease

- In the past: C. difficile linked to antibiotic use. Most cases treated successfully with metronidazole
- Diminished therapeutic response to metronidazole (50% failure rate with initial course of treatment).

**Epidemic strains of C. difficile**

700 *C. difficile* related deaths in Quebec, Canada in one year (2003-4)

400 *C. difficile* related deaths annually in Quebec at the present time

**BI/NAP1 Epidemic strain C. difficile**

- Regional outbreaks - Pittsburgh, PA, Quebec, Canada and the mid-Atlantic and southeastern U.S.

- *C. difficile* in low risk populations - young individuals, peripartum women, community dwelling and in individuals with no exposure to antibiotics.

C. difficile Epidemic in U.S.

BI/NAP1 C. difficile in U.S. Nov. 2007 (n = 38)

BI/NAP1 C. difficile in U.S. Oct. 2008 IDSA Meetings

Current burden of C. difficile in U.S.

- October 2008 – BI/NAP1 has been isolated in all 50 states (IDSA).
- Total number of C. difficile cases annually in U.S. is >500,000. Cost of $1.1 billion.
- Total number of C. difficile related deaths annually in the U.S. is >15,000.
- Epidemic is predicted to worsen.
- Cause?
Where does the majority of antibiotic use occur in the U.S.?

Antibiotic use in food animal industry

- Poultry industry – antibiotic use to prevent diarrheal illness
- Corn fed beef require antibiotics to prevent bacterial overgrowth
BI/NAP1 Epidemic strain *C. difficile* and food animals

- Colonization and carriage with the epidemic strain *C. difficile* (B1 NAP1 strain) reported in cows.

- *C. difficile* has been isolated from retail ground meat purchased in Canada.


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*C. difficile* infectious inoculum is 10 spores

*C. difficile* spores may be resistant to cooking. Source of bacterial food poisoning?

Poutanen SM et al. CMAJ. July 6, 2004;171(1).
1) Antibiotic destroys normal bacterial flora
2) *C. difficile* grows and secretes toxins
3) Toxins inflame and ulcerate mucosa
4) Damaged mucosa secretes fluid causing diarrhea

**C. difficile: Pathogenic mechanisms**

Poutanen SM et al. CMAJ. July 6, 2004;171(1).

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**II. Impact of C. difficile on IBD**

*Clostridium difficile*
**Clostridium difficile and IBD**

- *C. difficile* and IBD present in identical fashion ranging from mild diarrhea to fulminant colitis.
- Early studies performed 2 decades ago indicated little overlap between *C. difficile* and IBD, concluding “No need for routine screening for *C. difficile* in IBD population”.
- Recent studies: Increasing incidence and severity of *C. difficile* in IBD population
- *C. difficile* recently identified to have a significant negative impact on IBD morbidity.


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**Increasing Impact of Clostridium difficile on IBD**

![Graph showing increasing impact of *Clostridium difficile* on IBD from 1998 to 2005.](image)
Increasing Proportion of *Clostridium difficile* Patients With IBD

![Graph showing the increase in proportion of *Clostridium difficile* patients with IBD from 2000 to 2005.](image)

Complications: *Clostridium difficile* Infected Patients With IBD*

![Graph showing hospitalizations and colectomies from 1998 to 2005.](image)


Endoscopic Appearance of C. difficile

Endoscopic appearance of C. difficile in control patients

Endoscopic appearance of C. difficile in patients with IBD

Ulcerative Colitis

Crohn’s Disease

Histologic appearance C. difficile in IBD

Control patient

Crohn’s disease patient

Classic pseudomembrane on histology—mucin, fibrin, necrotic debris

Extensive cryptitis, crypt abscesses in Crohn’s colitis pt with active C. difficile. No inflammatory pseudomembranes are identified.

Demographic Data: IBD Patients With C. difficile

- 91% Colonic IBD
- 61% Recent antibiotic exposure


Clostridium difficile in IBD: Morbidity and Mortality

IBD patients with C. difficile compared with IBD alone:
- Longer hospital stay
- Increased hospitalization costs
- Higher colectomy rates
- Increased mortality rate –
- 118 IBD C.diff deaths in NIS 2004
- (>500 IBD C.diff deaths in U.S. 2004)

**C. difficile and IBD: Summary**

*Clostridium difficile* and IBD

- Patients with colitis are at increased risk
- Maintenance immunosuppression correlated with infection (purine analogs, methotrexate)
- 10% of cases were new IBD presentations
- Contributes to flare in setting of new and longstanding disease in remission
- Recommend multiple stool samples for ELISA toxin A, B analysis. 54% of patients detected on first stool sample.
- No prompt response to metronidazole, consider vancomycin p.o.


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**III. Diagnostic considerations:**

*C. difficile* in IBD

- Laboratory
  - Leukocytosis
  - Hypoalbuminemia
- Radiographic
- Endoscopy - Pseudomembranes in 50% of patients with CDAD – rare in IBD patients.
Cell culture toxin assay is the gold standard
- excellent sensitivity
- requires 24 – 48 hrs; labor intensive and expensive

ELISA for toxin A and B
- More rapid, less expensive and requires less expertise
- Sensitivity varies from 79% to 97%.

Stool ELISA testing in IBD patients for C. Difficile toxins A and B

4 stool samples to reach 90% detection with ELISA

Special IBD scenarios with *C. difficile*

**C. difficile** in ileo-anal Pouchitis

Two case reports
- Chronic refractory pouchitis
- Unresponsive to broad spectrum antibiotics
- In both cases *C. difficile* developed while patients were on metronidazole therapy

**C. difficile** in segments of diverted bowel

- One case report of *C. difficile* in UC pt following subtotal colectomy with end-ileostomy.
- Treated successfully with 10 day course of metronidazole suppositories.


**C. difficile** enteritis: An early complication in IBD patients following colectomy

- Rare but associated with significant morbidity with mortality rates ranging from 60-83%

IV. Therapeutic considerations: 
*C. difficile* in IBD

- *C. difficile* isolation and contact precautions.
- Daily stool testing for *C. difficile* (until positive sample). Possibility for in-hospital acquisition.
- Empiric oral vancomycin from day 1, alone or in combination with metronidazole (IV or po).
- Maintain oral diet!
- Decrease corticosteroid dosing – steroids blunt humoral immunity and IgG response to toxin A is necessary to resolve CDAD.

Approach for hospitalized IBD patients with Suspected/confirmed *C. difficile*
**Oral vancomycin vs metronidazole for C. difficile**

<table>
<thead>
<tr>
<th></th>
<th>VANCOMYCIN</th>
<th>METRONIDAZOLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Colonic levels</td>
<td>&gt; 500 mcg/ml</td>
<td>0-10 mcg/ml</td>
</tr>
<tr>
<td>Effectivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
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<tr>
<td>Promotion of VRE</td>
<td>Superior</td>
<td>Inferior</td>
</tr>
<tr>
<td>Failure rate</td>
<td>4%</td>
<td>13-16%*</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>10-25%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Side effects</td>
<td>Limited</td>
<td>Significant</td>
</tr>
<tr>
<td>Response (median time)</td>
<td>3 days</td>
<td>4.6 days</td>
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Cost:

- Oral vancomycin vs metronidazole for C. difficile
- Only FDA approved drug for the treatment of C. difficile
- Tablets of vancomycin – shortages in past, high cost
- Parenteral (intravenous formulation) vancomycin for oral use
- Decreased cost – involves hospital pharmacy formulation
- Palatability can be improved
  - mouthwash “chaser”
  - Apple juice “chaser”
- Parenteral vancomycin for enema formulation
Use of combination immunosuppression in setting of IBD and *C. difficile*

- Retrospective study from 20 ECCO investigators
- 155 IBD patients with *C. difficile* (59% UC)
  - Antibiotics alone (n = 51)
  - Combination Immunomodulator + antibiotic (n = 104)
- 12 colectomies, all in combination group
- Patients in combination group were sicker
  (more UC, abd pain, diarrhea, bleeding)
- Among colectomy patients:
  - Corticosteroids – 92%
  - Thiopurine/MTX - 42%
  - CsA - 33%
  - Anti-TNF 25%
  - Double/triple IS – 66%


Decreasing colectomy rate among hospitalized IBD patients with *C. difficile*

Number of infections and rate of hospitalization remained constant, but significant decrease in colectomy rate.
- High index of suspicion
- Use of oral vancomycin
- Decreased corticosteroid dosing

Preventive strategies - *C. difficile*

**Prophylaxis**
- Limit exposure to antibiotics
- MacFarland *et al.* Probiotics (*Saccharomyces boulardii*, *Lactobacillus rhamnosus GG*, and probiotic mixtures) effective for the prevention of CDAD (OR 0.59). data was strongest in *S. boulardii*
- Environmental decontamination requires 10% sodium hypochlorite solutions.
- Alcohol based hand gels are in-effective against spore-forming organisms. Soap and water dislodges spores from skin.
- Educate parents of newborns regarding handwashing following diaper changing.


**Refractory and recurrent *C. difficile***

**Refractory *C. difficile***:
- Intravenous immunoglobulin was used in a series of 14 patients (200 mg/kg).
  - 64% responded. One patient required 2nd dose.
- Consideration for hypogammaglobulinemia associated IBD.

**Recurrent *C. difficile***:
- 59% of IBD patients (27 out of 46) had a recurrence.
  - Of the recurring patients, one-quarter required colectomy.

*C. difficile* treatment regimens used:
1. Prolonged courses of vancomycin with or without pulse dosing (2 months)
2. Initial course of vancomycin followed by rifaximin maintenance course.

Cytomegalovirus (CMV) and IBD

Herpes virus family member.
Trophic to endothelial cells in microcirculation.
Life long latency following a primary infection.
CMV infections in immunosuppressed patients are reactivation.
CMV may be a nonpathogenic bystander or true pathogen.

Why IBD patients are at high risk for CMV

Pro-inflammatory cytokines (i.e. TNF) increased in active IBD mucosa trigger reactivation of CMV.

CMV tropism for sites of severe inflammation.

CMV reactivation with immunosuppressive medications especially corticosteroids.

Impact of CMV on IBD

CMV infection in IBD - associated with poor outcomes including colectomy.

Prevalence of CMV infections 5-30%
- worst in steroid refractory patients.

Although prevalence is high in active IBD it has been difficult to evaluate the real clinical impact of CMV infections.

Cottone M et al, Am J Gastro, 2001;96:773-775
Criscuoli V et al, Dig Liver Dis, 2004;36:818-820
Kishmore J et al, J Med Micro, 2004;1155-1160
Wada Y et al, Dis Colon Rectum, 2003;46:559-65

Diagnosis: CMV in IBD

Clinical findings:
- High index of suspicion
- Anemia
- Hypoalbuminemia

Endoscopic findings:
- Punched out ulcers

Histologic biopsies:
- H&E staining - viral inclusion bodies
- Immunohistochemistry - CMV antibody
- CMV DNA by PCR
Serology: CMV in IBD

Indirect evidence of recent CMV infection based upon change in antibody titers

ELISA, latex agglutination, radioimmunoassay, complement-fixation

Diagnosis of recent or acute CMV is probable if:
- CMV-specific IgM antibodies detected
- 4-fold increase in CMV-specific IgG titers in paired specimens 2 - 4 weeks apart

Helpful in determining past exposure to CMV infections.

Challenges in CMV diagnosis

IgM antibody persists for several months and therefore can provide misleading information if a prior baseline test not available.

Requires paired serum samples (IgG) - limits utility in establishing timely diagnosis.

Helpful in determining past exposure to CMV infections.
**CMV diagnosis: Alternative tests**

CMV antigenemia assays - rapid detection of CMV proteins in peripheral leukocytes using tagged monoclonal antibodies to the pp65 matrix protein of CMV in peripheral blood.

Reported as # of cells with staining per total # of cells counted (low # of positive cells).

Sensitivity and specificity are 90 and 96.

Results in 24 hrs.


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**Treatment: CMV colitis in IBD**

Discontinue/decrease immunosuppressives and taper steroids.

Ganciclovir:

- IV 5mg/kg BID X 14 days then
- Oral Valganciclovir 450 mg BID X 4 Weeks.

Monitor response with CMV pp65 antigenemia assays.
2 hospitalized
1 colectomy

*C. difficile* - 29 cases from 2002 – 2007.
16 hospitalized
7 colectomies

§ *C. difficile* has doubled in North American Medical Centers in the past 5 years.
§ IBD colitis patients have been affected at highest rate.
§ *C. difficile* in IBD is associated with high rates of hospitalization and colectomy and increased mortality.
§ Antibiotic use may not be required to precipitate infection.
§ Endoscopic and Histologic appearance is frequently not classical – pseudomembranes not always present.
§ Multiple stool ELISA samples for toxin analysis are required to make a diagnosis.
Summary and Conclusions - II

- Metronidazole failure rate is 50%; Oral vancomycin may be superior in hospitalized patients.
- *C. difficile* enteritis may occur in post-colectomy patients and patients with ileoanal reconstruction.
- *C. difficile* recurrence rates are high.
- Hand washing with soap and water is essential to prevent nosocomial transmission.

Summary and Conclusions - III

- CMV in IBD patients – occurs in patients with maximum immunosuppression and steroids. Transplant patient setting.
- Rate of infection is variable.
- Reactivation is most likely mechanism.
- Diagnosis based on punched out ulcers, histology for CMV.
- Treat with ganciclovir and decreased immunosuppression.